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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,060	YU, BAOFA	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-37,39,40,42-48,50,53,57,69 and 71-79* is/are pending in the application.

4a) Of the above claim(s) *1-35 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) *36,37,39,40,42,43,45-48,50,69,71 and 73-77* is/are allowed.

6)☐ Claim(s) *44,72 and 79* is/are rejected.

7)☐ Claim(s) *53 and 57* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 38, 41, 49, 51, 52, 54-56, 58-68 and 70 have been canceled. Claims 1-37, 39, 40, 42-48, 50, 53, 57, 69 and 71-79 are pending. Claims 1-35 and 78, drawn to non-elected inventions, remain withdrawn from consideration. Claims 45, 46 and 53, previously withdrawn as being drawn to non-elected species are now joined to the claims 36, 37, 39, 40, 42-44, 47, 48, 50, 57, 69, 71-77 and 77 for consideration at this time.

2. Applicant has amended claim 36 to incorporate the specific embodiments of claim 68 which were free of the prior art. It is noted that the species election of Paper No. 7 resulted in the election of the species of "liver" from those neoplasms recited in claim 72, and the species of "radiation sensitizer" from the species recited in claim 79. All species recited in claims 72 and 79 will be considered at this time.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action

4. Claim 72 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 72 recites "bruccal" as a type of neoplasm to be treated. It is unclear what the metes and bounds of the claim encompasses as "bruccal" is not a known tissue type or organ. For purpose of examination, bruccal will be read as "buccal".

5. Claim 79 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 79 recites "cytolytic gene sequence". The specification does not provide a definition to set the metes and bounds of genes sequences which constitute cytolytic gene sequences. It is unclear if a cytolytic gene sequence would encode a protein able to inflict direct cytotoxicity on a cell, such as perforin (Paul, Fundamental Immunology (text), 1993, pages 990-992) or the pore-forming components of complement (Paul, ibid, page 930, Table 5), or if cytolytic gene sequence is a gene sequence is a foreign antigen which causes an immune system

response to include the activation and recruitment of cytolytic cells such as cytotoxic T-lymphocytes and natural killer cells. For purpose of examination, all alternatives will be considered.

6. Claim 79 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 79 embodies the method of claim 36 wherein said method further comprises the administration in situ of a cytolytic gene sequence. It is noted that at the time of filing the art teaches numerous suicide gene sequences, cytokine gene sequences, cytokine depots and radiation sensitizers. further, reporter gene sequences and reporter combinations such as chloramphenicol and chloramphenicol transferase are well known in the art. However, only one reference in the literature has been identified encompassing cytolytic genes (the abstract of Schneider et al, Gene Ther, 1999, Vol. 6, suppl. 1, S5). this reference describes gene sequences comprising epitopes of measles antigen fused to epidermal growth factor or somatomedin-C. It is noted that claim 79 is rejected under 112, second paragraph for lacking metes and bounds. When given the broadest reasonable interpretation, the method claim is reliant upon a genus of "cytolytic genes" which is highly variant as it encompasses proteins which both induce cytolytic activity via upregulation of the immune response, and proteins which have direct cytolytic activity as complement pore-forming proteins and perforin of cytotoxic lymphocytes and natural killer cells. The specification does not define the constitution of a cytolytic gene sequence or the protein[s] encoded thereby. Thus, the genus encompasses by "cytolytic genus" is highly variant encompassing genes encoding proteins which are not structurally or functionally related. The specification does not set forth a working example of a cytolytic gene sequence. One of skill in the art would conclude that applicant was not in possession of the method claim reliant upon the genus of cytolytic sequences.

7. Claim 79 is are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising the administration of a cytokine containing depot,

does not reasonably provide enablement for methods comprising the administration of a suicide gene sequence, a cytolytic gene sequ3nce, a cytokine gene sequence, a reporter, a reporter gene sequence or a radiation sensitizer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

(A) As drawn to a radiation sensitizer

Claim 79 recites the limitation of administering a radiation sensitizer as part of the method of claim 36. It is noted that claim 36 has been amended to delete reference to a coagulation "treatment". The art teaches laser treatment of neoplasms in combination with the administration of a radiation sensitizer to induce coagulation (Dima et al, Laser Therapy, 1990, Vol.2, pp. 153-160, cited in the previous Office action). The specification does not provide any guidance of how to use a "radiation sensitizer" outside of the context of laser coagulation treatment. Therefore, without the specific embodiment of "coagulation treatment" recited in claim 36, one of skill in the art would not know how to use the method of treatment of claim 79 drawn in part to the administration of a radiation sensitizer.

(B) As drawn to methods comprising the administration of gene sequences

Claim 79 specifically embodies the in situ administration of gene sequences. This claim clearly encompasses gene therapy and the specification is not enabling for such methods for the reasons set forth below.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed gene sequences. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of

mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

It is well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or a tumor in situ is in the realm of gene therapy, and highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"). Orkin et al conclude that, "none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the gene sequences within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the method of claim 79.

It is also noted that claim 79 is drawn to a reporter and a reporter gene sequence. The art defines a reporter gene as a promoterless gene whose expression is used as an indication of transcriptional activity of another gene after its fusion of the gene of interest (for instance see Reiger et al, Ed.s, Glossary of Genetics, Classical and Molecular, fifth Edition, 1991, page 422). Thus, in order to use said system, one of skill in the art would need to know the potential "gene of interest" in order to make the fusion construct with the reporterless gene, and further one of skill in the art would have to have some reasonable expectation of success that the gene of interest would be activated by a particular transcriptional activator which would be present in the cells undergoing the claimed method of treatment. However, the specification does not teach the diagnostic or therapeutic benefit of administering said gene sequences, nor does it teach "a gene of interest" or the activation of a gene of interest by transcriptional activators. Further, the specification does not teach how to use the information obtained from the activator of said reporter gene in a method of treatment. Given these lack of teachings one of skill in the art would not be able to make or use the reporter and reporter gene sequence in the instant method claim.

8. Claim 72 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for treating neoplasms consisting of adrenal gland, anus, bile ducts, bladder, bone, breast, b[r]uccal, cervix, colon, ear, endometrium, esophagus, eyelids, fallopian tube, gastrointestinal tract, head and neck, heart, kidney, larynx, liver, lung, mandible, madibular condyle, maxilla, mouth, nasopharynx, nose, oral cavity, ovary, pancreas, parotid gland, penis, pinna, pituitary, prostate gland, rectum, salivary glands, skin, small intestine, stomach, testes, thyroid, tonsil, urethra, uterus, vagina and vulva neoplasm does not reasonably provide enablement for methods of treating neoplasms consisting of auditory nerve, brain, central nervous system, eye, , spinal cord, , vestibulocochlear nerve. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 72 is drawn to methods of treating numerous types of neoplasia by means of the instant method comprising the administration of the hapten TNP, hydrogen peroxide and ethanol to a neoplasm in situ. The specification teaches on page 5, lines 16-24 that the instant method of

treatment "creates an area of inflammation that attracts lymphocytes and other inflammatory response mediators to the target tumor sites. the attracted lymphocytes include tumor antigen presenting cells, macrophages, dendritic cells and activated B-cells, The lymphocytes are exposed to tumor antigens generated from tumor cells lysis and elicit a tumor specific response". Thus, the specification. Claim 72 recites tissues and organs that are which encompass those tissues and organs which are known to be subject to immunological privilege, such as eye and central nervous system tumors. It is well known in the art that eye and the nervous system is protected from bodily inflammation and the mounting of an immune response.

It is taught by the prior art that the nervous system is lacking in antigen presenting cells and it without lymphatic drainage, thus, the ability to generate antigen primed T-cells is compromised and also that neurons are lacking in MHC expression and even in the presence of inflammatory lymphokines can only express low levels of MHC class I molecules, thus limiting the initiation of CD+8 T cell responses (Paul, Fundamental Immunology, (text), 1993, pp. 705-706). It is noted that in the post filling date reference (abstract, Ferguson et al, Int Review Immunol, 2002, Vol. 21, pp. 153-172, lines 9-12)it is stated that an immune response in immunologically privileged tissues either does not proceed or proceeds in a manner different from other areas. The specification provides specific examples of the treatment of liver, esophagus, ovary, breast, pancreatic, colon cancers. The specification does not provide specific examples of treatment of brain, eye or other nervous system tumors. Given the teachings of the art regarding the immune response in the eye and nervous tissues, one of skill in the art would not expect a nexus between the response of liver, esophagus, ovary, breast, pancreatic, colon cancers to the instant methods and the response of the eye and the nervous tissues to the instant treatment methods. Furthermore, it is noted on page 2, lines 22-23 that the specification teaches "Alcohol cannot be injected close to critical structures such as the central nervous system". Claim 72 is dependent upon claim 36 which contains the specific embodiment of the administration of ethanol. One of skill in the art would not be able to practice the method of claim 72 as drawn to nervous system tissue and the eye because it can be concluded from the art that the generation of an immune response in said tissues is not the same as the generation of an immune response in another tissues not at immunologically privileged sites and additionally

because the administration of ethanol to the central nervous system appears to conflict with the teachings of the specification.

9. Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant method claim is reliant upon a group of immune response potentiators comprising an enzyme, a non-virulent virus, a polysaccharide and a herb extract. When given the broadest reasonable interpretation each of an enzyme, a non-virulent virus, a polysaccharide and a herb extract read on a separate genus of compounds. The specification describes VCN, papain, beta-Gal and ConA as enzymes which are immune response potentiators. The specification describes the Newcastle virus as a non-virulent virus which is an immune response potentiator. The species of enzyme, non-virulent virus and herb extract are widely variant encompassing proteins, viruses and compounds having different structural and functional attributes and including immune response potentiators including enzymes, non-virulent viruses and herb extracts yet to be discovered. The specification fails to teach how the description of VCN, papain, beta-Gal and ConA as enzymes which are immune response potentiators relates to other enzymes which would have immunomodulatory properties. Likewise the specification fails to relate the Newcastle disease virus to other viruses which are non-virulent and have the property of being immunomodulators. One of skill in the art would conclude that applicant was not in possession of the genus of enzymes as immune response potentiators as a description of VCN, papain, beta-Gal and ConA is not representative of the variants of the genus. One of skill in the art would conclude that applicant was not in possession of the genus of non-virulent viruses as a description of the Newcastle disease virus is not representative of all the species of the claimed genus.

The specification fails to describe a herb extract having the properties of an immune response potentiator, neither the herb, nor the method of extraction are described in the specification, nor is there a description of compounds which are present in said extract which would ct as a immmunomodulator. .Although drawn to DNA arts, University of California v. Eli

Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant method claim. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

In this case, the specification does not describe the herb from which the extract is made, the extraction procedure, or the compounds present in the extract which would have the characteristics of an immuno modulator in a manner that satisfies either the Lilly or Enzo standards. Thus, the specification does not provide an adequate written description of the herbal extract having immunomodulatory properties. Since the specification fails to adequately describe the product on which the claimed, method is based it also fails to adequately describe the claimed method.

10. Claims 53 and 57 are objected to as being dependent upon a canceled base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. All other rejections and objection as set forth in Paper No. 13 are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
9/22/03